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(54) Title: FARNESYL TRANSFERASE INHIBITORS IN COMBINATION WITH HMG CoA REDUCTASE INHIBITORS FOR THE TREATMENT OF CANCER

(57) Abstract

The present invention relates to a method of treating cancer in a mammal, including a human, by administering to the mammal a FTase inhibitor in combination with an HMG CoA reductase inhibitor.

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FARNESYL TRANSFERASE INHIBITORS IN COMBINATION WITH HMG CoA REDUCTASE INHIBITORS FOR THE TREATMENT OF CANCER

This invention relates to the use of a farnesyl transferase (FTase) inhibitor in combination with a hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor to treat cancer in a mammal.

Oncogenes are genes that, when activated, encode protein components of signal transduction pathways which lead to the abnormal stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells.

Mutation and/or overexpression of certain oncogenes is frequently associated with human cancers and other disorders involving abnormal (i.e., unregulated) cell growth. For example, the growth of benign and malignant tumors can be caused by the expression of an activated *Ras* oncogene or by activation of the *Ras* protein by another gene that has undergone oncogenic mutation. The abnormal growth of cells that occurs in the benign and malignant cells of other proliferative disorders can be caused by aberrant *Ras* activation. Mutated, oncogenic forms of *Ras* are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993). The *Ras* oncogene is expressed in about 40% of solid malignant tumors that are unresponsive to conventional chemotherapies. The K-*Ras* isoform is expressed in about 90% of pancreatic tumors and about 40% of colorectal and lung cancers. The H-*Ras* isoform is expressed in about 40% of head and neck cancers. The N-*Ras* isoform is expressed in most thyroid cancers and about 25% of acute myeloid leukemias. To acquire the potential to transform normal cells into cancer cells or benign cells that exhibit abnormal growth, as defined below, the precursor of the *Ras* oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, are therefore useful as anticancer agents for tumors in which *Ras* contributes to transformation.

The K-*Ras* isoform can be both farnesylated and geranyl-geranylated in intact cells. Potent inhibitors of the enzyme farnesyl (FTase) that are highly selective for FTase versus geranylgeranyl transferase I (GGTase I) can be incapable of blocking prenylation of mutant K-*Ras* and therefore ineffective at inhibiting growth of K-*Ras* expressing tumor cells.

The present inventor has found that the administration of a low dose HMG CoA reductase inhibitor in combination with a potent selective FTase inhibitor will block K-*Ras* prenylation and K-*Ras* function, as well as H-*Ras* prenylation and function. The activity of the protein prenyl transferases FTase and GGTase I is dependent on the concentrations of the

isoprenoid substrates, farnesyl- and geranylgeranyl-pyrophosphates, respectively. Mevalonate is the first committed intermediate in the isoprenoid pathway, and its synthesis is dependent on the activity of HMG CoA reductase. Compounds such as lovastatin and compactin, which are tight binding inhibitors of HMG CoA reductase, block mevalonate formation and thus block the isoprenoid pathway. They therefore inhibit both FTase and GGTase I.

The therapeutic effect of compounds from the two above classes of drugs (FTase inhibitor and HMG CoA reductase inhibitor) is believed to be synergistic. The present inventor has found that the combined administration of an FTase inhibitor and an HMG CoA reductase inhibitor overcomes the limitations of each given separately. The combination is therefore expected to be effective in cases where either agent alone would not be effective.

Japanese Patent Application JP7316076A, which was published on December 5, 1995, refers to an anticancer pharmaceutical composition that contains limonene, which, while not a FTase inhibitor, has been shown to impair the incorporation of mevalonic acid-derived isoprene compounds into *Ras* and *Ras* related proteins, and pravastatin, which is an HMG CoA reductase inhibitor.

The present invention relates to a pharmaceutical composition for the treatment of cancer or a benign proliferative disorder in a mammal, including a human, comprising a FTase inhibitor, an HMG CoA reductase inhibitor and a pharmaceutically acceptable carrier, wherein the active ingredients in such composition (i.e., the FTase inhibitor and the HMG CoA reductase inhibitor) are present in amounts that render the composition effective in the treatment of cancer or a benign proliferative disorder.

This invention also relates to a method of treating cancer or a benign proliferative disorder in a mammal, including a human, comprising administering to said mammal an anticancer or antiproliferative effective amount of a pharmaceutical composition comprising a FTase inhibitor, an HMG CoA reductase inhibitor and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating cancer or a benign proliferative disorder in a mammal, including a human, comprising administering to said mammal a FTase inhibitor and an HMG CoA reductase inhibitor in amounts that render the combination of such two active agents effective in the treatment of cancer or a benign proliferative disorder.

This invention also relates to a pharmaceutical composition for inhibiting the abnormal growth of cells in a mammal, including a human, comprising a FTase inhibitor, an HMG CoA reductase inhibitor and a pharmaceutically acceptable carrier, wherein the active ingredients in such composition (i.e., the FTase inhibitor and the HMG CoA reductase inhibitor) are present in amounts that render the composition effective in inhibiting the abnormal growth of cells.

This invention also relates to a method of inhibiting the abnormal growth of cells in a mammal, including a human, comprising administering to said mammal a FTase inhibitor and an HMG CoA reductase inhibitor in amounts that render the combination of such two active ingredients effective in inhibiting the abnormal growth of cells.

The term "treating, as used herein, refers to preventing, or retarding or inhibiting the progress of the disorder to which such term is applied.

"Abnormal cell growth", as used herein, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated *Ras* oncogene; (2) tumor cells in which the *Ras* protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant *Ras* activation occurs.

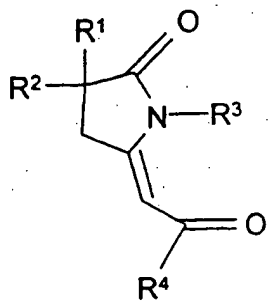
Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy and restenosis.

Patients that can be treated with a FTase inhibitor in combination with an HMG CoA reductase inhibitor according to the methods of this invention or using the pharmaceutical compositions of the invention include, for example, patients that have been diagnosed as having lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphona, spinal axis tumors, brain stem gliomas or pituitary adenomas).

Patients that can be treated with a FTase inhibitor in combination with an HMG CoA reduction inhibitor according to the methods of this invention or using the pharmaceutical compositions of the invention also include patients suffering from abnormal cell growth, as defined above.

More specific embodiments of this invention relate to the above pharmaceutical compositions and methods of treatment wherein the FTase inhibitor is selected from:

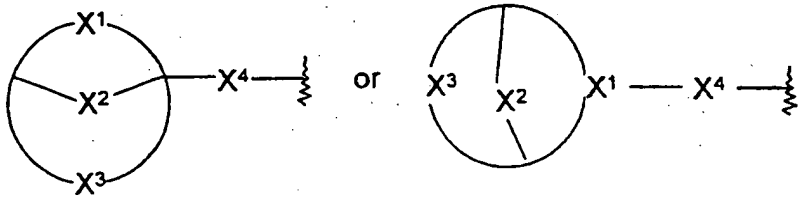
(a) compounds of the formula



I

wherein R^1 and R^2 are independently selected from the group consisting of $-(CH_2)_p$(5-10 membered heterocycles), $-(CH_2)_p(C_6-C_{10}$ aryl), allyl, propargyl and C_1-C_6 alkyl wherein p is 0 to 3, said alkyl and the alkyl moieties of said R^1 and R^2 groups are optionally substituted by 1 to 3 R^9 substituents, and the aryl and heterocyclic moieties of said R^1 and R^2 groups are optionally substituted by 1 to 3 substituents independently selected from halo and R^9;

R^3 is $-(CH_2)_m$(1- or 2-adamantyl), $-(CH_2)_m(C_3-C_{10}$ cycloalkyl), $-(CH_2)_m(C_6-C_{10}$ aryl), C_1-C_{10} alkyl,



(A) (B)

wherein m is 0 to 6, and said cycloalkyl and alkyl optionally contain 1 or 2 double or triple bonds;

X^1, X^2, and X^3 are each independently C_1-C_7 alkylene optionally containing 1 or 2 double or triple bonds, X^4 is a bond or C_1-C_7 alkylene optionally containing 1 or 2 double or triple bonds, and, in formula (B), the X^4 moiety is attached to the X^1 moiety at any available carbon in the X^1 moiety;

R^4 is C_6-C_{10} aryl, 5-10 membered heterocyclyl or C_1-C_6 alkyl wherein each of said R^4 groups is optionally substituted by 1 to 3 R^5 substituents;

each R^5 is independently selected from the group consisting of halo, nitro, cyano, phenyl, $-C(O)OR^6$, $-SO_2NR^6R^7$, $-NR^8R^8$, $-C(O)R^6$, $-OR^6$, $-C(O)NR^6R^8$, $-OC(O)NR^6R^8$, $-NR^8C(O)NR^8R^6$, $-NR^8C(O)R^6$, $-NR^8C(O)O(C_1-C_4$ alkyl), $-C(NR^8)NR^8R^6$, $-C(NCN)NR^8R^6$, $-C(NCN)S(C_1-C_4$ alkyl), $-NR^8C(NCN)S(C_1-C_4$ alkyl), $-NR^8C(NCN)NR^8R^6$, $-NR^8SO_2(C_1-C_4$ alkyl), $-S(O)_n(C_1-C_4$ alkyl) wherein

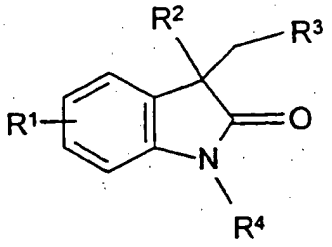
n is 0 to 2, $-NR^8C(O)C(O)NR^8R^6$, $-NR^6C(O)C(O)R^8$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, and C_1-C_4 alkyl optionally substituted by 1 to 3 fluoro substituents;

each R^6 and R^7 is independently hydrogen or C_1-C_4 alkyl;

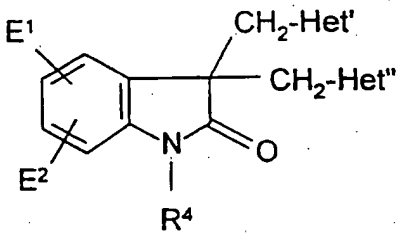
each R^8 is independently R^6 or $-OR^6$; and,

each R^9 is independently selected from cyano, R^6, $-OR^6$, $-OC(O)R^6$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6R^8$, $-SO_2NR^6R^7$, and C_1-C_4 alkyl substituted by hydroxy; and

(b) compounds of the formula



or



IIA IIB

wherein R^1 is hydrogen, halo (e.g., chloro, fluoro, bromo or iodo), cyano, hydroxy, nitro, trifluoromethyl, $-NHR^5$, $-NR^5R^5$, R^5, $-OR^5$ or $-S(O)_m-R^5$;

R^2 is $-(CH_2)_n-Y$ or $-OCOR^5$;

R^3 is 4-, 3-, or 2-pyridyl, pyrimidyl, pyrazinyl, 2-fluoro-4-pyridyl or 3-fluoro-4-pyridyl;

R^4 is 1-adamantyl or 2-adamantyl;

Y is hydrogen, hydroxy, amino, cyano, $-NHR^5$, $-NR^5R^5$, $-NHCOR^5$, $-NHCO_2R^5$, halo, OR^5, $-S(O)_mR^5$, $-CO_2H$, $-CO_2R^5$, $-CONR^5R^5$, $-CONHR^5$, $-CONH_2$, $-COR^5$, $-CH=CHCO_2R^5$, $-OCOR^5$, phenyl, phenyl substituted with W, $-C\equiv CCO_2R^5$, $-CH=CHR^5$ or $-C\equiv CR^5$;

each R^5 is, independently, (C_1-C_4) straight or branched alkyl, phenyl or benzyl, wherein said phenyl and the phenyl moiety of said benzyl may optionally be substituted with halo, hydroxy, nitro, cyano, amino, (C_1-C_4) straight or branched alkyl, (C_1-C_4) straight or branched alkoxy, phenyl, benzyl, (C_1-C_4)alkylamino, di[(C_1-C_4)alkyl]amino, or $-S(O)_m-(C_1$-$C_4)$ straight or branched alkyl;

each W is, independently, halo, R^5, hydroxy, $-OR^5$, nitro, amino, $-NHR^5$, $-NR^5R^5$, cyano, or $-S(O)_m-R^5$;

m is 0, 1 or 2;

n is 1 to 7;

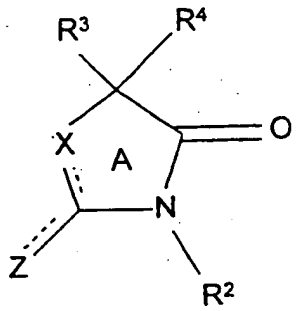
p is 0 or 1;

E^1 and E^2 are selected, independently, from hydrogen, halo, $(C_1$-$C_3)$alkyl, hydroxy, $(C_1$-$C_3)$alkoxy, nitro, trifluoromethyl, cyano, amino, $(C_1$-$C_3)$alkylamino and di[$(C_1$-$C_3)$alkyl]amino;

and their pharmaceutically acceptable salts.

Het' and Het'' are selected, independently, from 6 membered heterocyclic rings containing from one to four nitrogen atoms as part of the ring, optionally substituted with one substituent selected from $(C_1$-$C_3)$alkyl, halo, hydroxy, $(C_1$-$C_3)$alkoxy, amino, $(C_1$-$C_3)$alkylamino and di[$(C_1$-$C_3)$alkyl]amino; and

(c) compounds of the formula



III

wherein both dotted lines represent optional double bonds;

Z is oxygen or sulfur when it is double bonded to ring A and Z is hydroxy, $(C_1$-$C_{10})$alkyl-S-, $(C_1$-$C_{10})$alkyl-SO-, $(C_1$-$C_{10})$alkyl-SO_2-, adamant-2-yl-S-, naphthyl-S-, benzyl-S-, phenyl-C(=O)CH_2-S-, $(C_1$-$C_6)$alkyl-O-C(=O)-CH_2-S- or (H,H) (i.e., Z represents two hydrogen atoms, each of which is single bonded to the same carbon of ring A) when Z is single bonded to ring A, and wherein said naphthyl and phenyl and the phenyl moiety of said benzyl may optionally be substituted with from one to three substituents independently selected from $(C_1$-$C_6)$alkyl optionally substituted with from one to three fluorine atoms, $(C_1$-$C_6)$alkoxy optionally substituted with from one to three fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), amino, $(C_1$-$C_6)$alkylamino, [di-$(C_1$-$C_6)$alkyl]amino, cyano, nitro, $(C_1$-$C_6)$alkyl-SO_n- wherein n is zero, one or two, -COOH, -COO$(C_1$-$C_6)$alkyl and -C(O)NH$(C_1$-$C_6)$alkyl;

X is NR^1 or CHR^1;

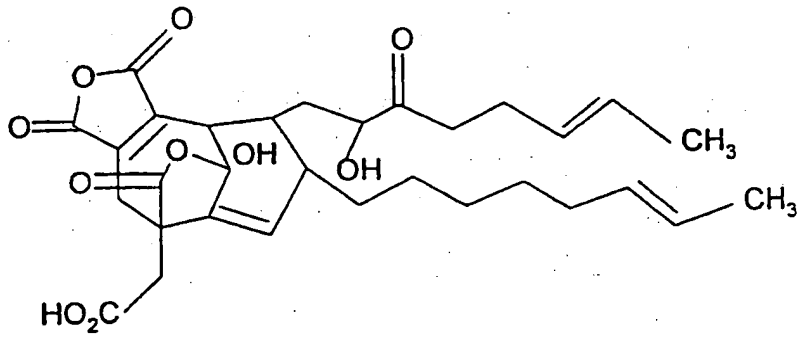
R^1 is hydrogen, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkylphenyl when ring A is saturated (i.e., when ring A contains no double bonds) and R^1 is absent when ring A contains a double bond;

R^2 is selected from naphthyl, phenyl, $(C_1$-$C_6)$alkylphenyl, 1-adamantyl, 2-adamantyl, $(C_1$-$C_8)$ straight or branched alkyl, $(C_3$-$C_{10})$ cycloalkyl and $(C_8$-$C_{30})$bicyclic or tricyclic alkyl; wherein said $(C_3$-$C_{10})$cycloalkyl and said $(C_8$-$C_{30})$bicyclic or tricyclic alkyl may optionally be substituted with a hydroxy group; and wherein said adamantyl groups may optionally be substituted with from one to three substituents independently selected from $(C_1$-$C_6)$alkyl, halo and hydroxy; and

R^3 and R^4 are independently selected from benzyl, wherein the phenyl moiety of said benzyl may optionally be substituted with an amino or nitro group; hydrogen, phenyl, $(N\equiv C)$-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-O-C(=O)-$(C_1$-$C_6)$alkyl and Het-CH_2, wherein Het is selected from 2-, 3- or 4-pyridinyl, furyl, tetrahydrofuryl, pyrimidyl, pyrazinyl, pyrazolyl, isoxazolyl, thiophenyl and triazolyl;

with the proviso that (a) no more than one of the two dotted lines can represent a double bond in any one compound, (b) when Z is (H, H), X is CH_2, (c) when Z is oxygen or (H, H) and X is CHR^1, R^1 must be hydrogen, (d) when Z is sulfur and X is NR^1, R^1 must be hydrogen, and (e) one of R^3 and R^4 must be Het-CH_2, and

(d) the compound



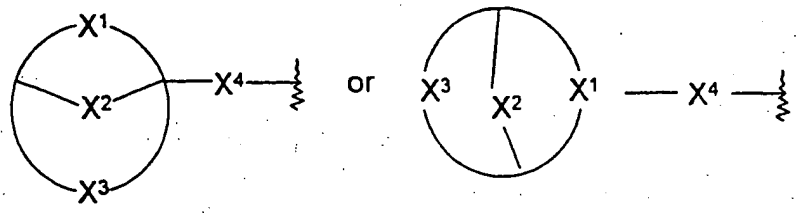
IV

and the pharmaceutically acceptable salts of the foregoing compounds.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the FTase inhibitor is selected from compounds of the formula I as defined above, wherein R^1 and R^2 are both -$(CH_2)_p$(5-10 membered heterocycles) wherein p is 1 or 2.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the FTase inhibitor is selected from compounds of the formula I as defined above, wherein R^3 is a -$(CH_2)_m$(pinane) wherein m is 0, 1 or 2, and, more preferably, those wherein R^3 is pinanemethyl.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the FTase inhibitor is selected from compounds of the formula I, as defined above, wherein R^3 is



(Ia) (Ib)

wherein X^1, X^2, X^3 and X^4 are as defined above.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the FTase inhibitor is selected from compounds of the formula I, as described above, wherein R^4 is phenyl optionally substituted by 1 to 3 R^5 substituents.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment, wherein the FTase inhibitor is selected from the compounds listed below:

2-[2-(4-Bromo-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

4-{[5-Oxo-4,4-bis-pyridin-4-ylmethyl-1-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

2-[2-(4-Chloro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(3,4-Dichloro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(3-Nitro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(4-Methoxy-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(3-Methoxy-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(2-Methoxy-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-(2-Biphenyl-4-yl-2-oxo-ethylidene)-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-(2-Naphthalen-2-yl-2-oxo-ethylidene)-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(4-Fluoro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(2,4-Difluoro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

4-{[5-Oxo-4,4-bis-pyridin-4-ylmethyl-1-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

2-[2-(4-Nitro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-Oxo-2-phenyl-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-{2-Oxo-2-[4-(2H-tetrazol-5-yl)-phenyl]-ethylidene}-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

3-{[5-Oxo-4,4-bis-pyridin-4-ylmethyl-1-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-{[5-Oxo-4,4-bis-pyridin-4-ylmethyl-1-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-2-ylidene]-acetyl}-benzoic acid ethyl ester;

2-[2-Oxo-2-(4-trifluoromethyl-phenyl)-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

2-[2-(4-Methanesulphonyl-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-3-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-imidazolidin-4-one;

4-{[1-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-[(1-Bicyclo[2.2.2]oct-1-ylmethyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-{[1-(2-Ethyl-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-{[1-(2-Benzyl-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-{[1-(2-Isopropenyl-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-{[1-(2-Isopropyl-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-({1-[2-(1-Methoxyimino-ethyl)-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl]-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene}-acetyl)-benzonitrile;

4-[[1-(6,6-Dimethyl-2-methylene-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-[[1-(2-Hydroxy-2-hydroxymethyl-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-[[1-(6,6-Dimethyl-2-oxo-bicyclo[3.1.1]hept-3-ylmethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

3-tert-Butyl-2-(2-oxo-2-phenyl-ethylidene)-5,5-bis-pyridin-4-ylmethyl-imidazolidin-4-one;

4-[[1-(2,2-Dimethyl-propyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-[[1-(2-Adamantan-1-yl-ethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

3-Cyclohexyl-2-(2-oxo-2-phenyl-ethylidene)-5,5-bis-pyridin-4-ylmethyl-imidazolidin-4-one;

4-[(1-Adamant-1-ylmethyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-[(1-Cyclohexylmethyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

3-Hexyl-2-(2-oxo-2-phenyl-ethylidene)-5,5-bis-pyridin-4-ylmethyl-imidazolidin-4-one;

3-Napthalen-1-yl-2-(2-oxo-2-phenyl-ethylidene)-5,5-bis-pyridin-4-ylmethyl-imidazolidin-4-one;

3-Adamantan-1-yl-2-(2-oxo-2-phenyl-ethylidene)-5,5-bis-pyridin-4-ylmethyl-imidazolidin-4-one;

3-Adamantan-1-yl-2-[2-(4-nitro-phenyl)-2-oxo-ethylidene]-5,5-bis-pyridin-4-ylmethyl-imidazolidin-4-one;

4-[(1-Benzyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-[(1-Allyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-[(1-Methyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-[[1-(2,2-Diethoxy-ethyl)-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene]-acetyl}-benzonitrile;

4-[(1-Adamantan-2-ylmethyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-[(1-Adamantan-2-yl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

4-[(5-Oxo-1-phenyl-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl]-benzonitrile;

and,

4-{[4-tert-Butyl-phenyl-5-oxo-4,4-bis-pyridin-4-ylmethyl-imidazolidin-2-ylidene)-acetyl}-benzonitrile.

and the pharmaceutically acceptable salts of such compounds.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the HMG CoA reductase inhibitor contained in such composition or used in such method is selected from the group consisting of atorvastatin, pravastatin, niacin, gemfibrozil, clofibrate, lovastatin, fluvastatin, simvastatin and compactin, and the pharmaceutically acceptable salts of the foregoing compounds.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the HMG CoA reductase inhibitor contained in such composition or used in such method is atorvastatin.

Other more specific embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the HMG CoA reductase inhibitor contained in such composition or used in such method is lovastatin.

Other more specific embodiments of this invention relate to any of the above the pharmaceutical compositions and methods of treatment wherein the FTase inhibitor contained in such composition or used in such method is selected from:

(a) compounds of the formula IIA, as defined above, wherein R^3 is 4-pyridyl, 4-pyrimidyl or 2-fluoro-4-pyridyl;

(b) compounds of the formula IIA, as defined above, wherein R^2 is $-(CH_2)_nY$;

(c) compounds of the formula IIA, as defined above, wherein R^2 is $-(CH_2)_nY$ and n is an integer from 1 to 5;

(d) compounds of the formula IIA, or IIB as defined above, wherein each of R^1, E^1, E^2 and R^4, if present, is hydrogen; and

(e) compounds of the formula IIA, as defined above, wherein R^2 is $-(CH_2)_n-Y$, R^1 is 4-pyridyl, 4-pyrimidyl or 2-fluoro-4-pyridyl, R^5 is (C_1-C_2) alkyl and Y is $-CO_2R^5$, cyano, $-CONHR^4$, $CH=CHCO_2R^5$ or $-OCOR^5$;

Other more specific embodiments embodiments of this invention relate to any of the above pharmaceutical compositions and methods of treatment wherein the FTase inhibitor contained in such composition or used in such method is not limonene or d-limonene.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "halo", as used herein, refers to chloro, fluoro, bromo or iodo.

The above compounds of the formulas I, IIA, IIB, III and IV may contain one or more chiral centers and therefore may exist in 2 or more enantiomeric and diastereomeric forms. The

above definitions of the compounds having formulas I, IA, IIB, III and IV include all enantiomers, diasteriomers and other stereoisomers of these compounds, as well as mixtures thereof.

The following references refer to compounds that exhibit activity as FTase inhibitors and which can be used, in combination with an HMG CoA reductase inhibitor, in the pharmaceutical compositions and methods of this invention, and to methods of preparing the same: International Patent Application PCT/US92/11292, which designates the United States and was published on July 22, 1993 as WO 93/14085; United States Patent 4,876,259, which issued on October 24, 1989; United States Patent H1345 which issued on August 2, 1994; United States Patent 5,260,332, which issued on November 9, 1993; United States Patent 5,262,435, which issued on November 16, 1993; United States Patent 5,369,125, issued on November 29, 1994; World Patent Application WO 93/24633, which was published on December 9, 1993: World Patent Application WO 94/03597, which was published on February 17, 1994; World Patent Application WO 94/16069, which was published on June 21,1994; G.L. Bulton, et al., 209th American Chem. Soc. Nat'l Meeting, Anaheim, Ca, April 2-6, 1995, Division of Med. Chem., Abs. No. 032, World Patent Application WO 95/00497, which was published on January 5, 1995; United States Patent 5,260,479, which was published on November 9, 1993; World Patent Application WO 95/10514; World Patent Application WO 95/10515; World Patent Application WO 95/10516; World Patent Application WO 95/12572, which was published on May 11, 1995; World Patent Application WO 95/11917, which was published on May 4, 1995; World Patent Application WO 94/26723, which was published on November 24, 1994; World Patent Application WO 95/25086, which was published on September 21, 1995; Kanda et al, AFMC. International Medicinal Chemistry Symposium AIMECS 95, Tokyo, Japan, Poster, P7M153, Sept. 4, 1995; World Patent Application WO 96/10037 which was published on April 4, 1996; World patent Application 96/10035, which was published on April 4, 1996; World Patent Application WO 96/10034, which was published on April 4, 1996; World Patent Application WO 96/10011, which was published on Apri 6, 2996; World Patent Application WO 96/10011, which was published on April 6, 1996; World Patent Application WO 96/09821, which was published on April 4, 1996; World Patent Application WO 96/09820, which was published on April 4, 1996; Quin et al, 211th American Chemical Society National Meeting, New Orleans, La., March 24-28, 1996, Lecture, COMP 012, March 24, 1996; World Patent Applications WO 96/06609 and WO 96/06604, both of which were published on March 7, 1996; European Patent Application EP 696,593, which was published on February 14, 1996; Hartman, G. D., 14th International Symposium on Medicinal Chemistry, Maastricht, Netherlands, September 8-12, 1996, Lectura, SL-08.3, Sept. 10, 1996; World Patent Application WO 96/30363, which was published on October 3, 1996; World Patent Application WO 96/30343, which was published in October 3, 1996, World Patent Application WO 97/03050; World Patent Application WO 94/26723, which was published on November 24, 1994; International Patent

Application PCT/IB95/00189, which designates the United States and was filed on March 20 1995; United States Patent Application 08/236,743, which was filed on April 29, 1994; United States Provisional Application entitled "Adamantyl Substituted Oxindoles As Pharmaceutical Agents," which was filed on May 28, 1996, in the name of R.A. Volkmann and J.P. Lyssikatos; United States Patent 5,350,867, which issued on September 27, 1994; United States Patent 5,352,705, which issued on October 4, 1994; United States Patent 5,565,489, which issued on October 15, 1996; European Patent Application EP 750,609, which was published on January 2, 1997; European Patent Application 461,869, which was published on December 18, 1991; and World Patent Application 96/21456, which was published on July 18, 1996.

The following references refer to compounds that exhibit activity as HMG CoA reductase inhibitors and which can be used, in combination with a FTase inhibitor, in the pharmaceutical compositions and methods of this invention, and to methods of preparing the same: United States Patent 4,681,893, issued July 21, 1987; United States Patent 5,273,995, issued December 28, 1993; United States Patent 5,385,929, issued January 31, 1995; United States Patent 4,957,971, issued September 18, 1990; United States Patent 5,102,893, issued April 7, 1992; United States Patent 4,957,940, issued September 18, 1990; United States Patent 4,950,675, issued August 21, 1990; United States Patent 4,929,620, issued May 29, 1990; United States Patent 4,923,861, issued May 8, 1990; United States Patent 4,906,657, issued March 6, 1990; United States Patent 4,868,185, issued September 19, 1989; United States Patent 5,124,482 issued June 23, 1992; United States Patent 5,003,080, issued March 26, 1991; United States Patent 5,097,045, issued March 17, 1992; United States Patent 5,149,837, issued September 22, 1992; United States Patent 4,906,624, issued March 6, 1990; United States Patent 4,761,419, issued August 2, 1988; United States Patent 4,735,950, issued April 5, 1988; United States Patent 4,808,621, issued February 28, 1989; United States Patent 4,647,576, issued March 3, 1987; United States Patent 5,118,882, issued June 2, 1992; United States Patent 5,214,197, issued May 25, 1993; United States Patent 5,321,046, issued June 14, 1994; United States Patent 5,260,440, issued November 9, 1993; and United States Patent 5,208,258 issued May 4, 1993; United States Patent 5,369,125, issued November 29, 1994; United States Patent H1345 issued August 2, 1994; United States Patent 5,262,435, issued November 16, 1993; and United States Patent 5,260,332, issued November 9, 1993. Great Britian Patent Application GB 2,055,100, published February 25, 1981; United States Patent 4,499,289, issued February 12, 1983; United States Patent 4,645,854, issued February 24, 1987; United States Patent 4,613,610 issued September 23, 1986; United States Patent 4,668,699, issued May 26, 1987; United States Patent 4,851,436, issued July 25, 1989; United States Patent 4,678,806, issued July 7, 1987; United States Patent 4,772,626, issued September 20, 1988; United States Patent 4,855,321, issued August 8, 1989;

European Patent Application EP 244364, published November 4, 1987; United States Patent 4,766,145, issued August 23, 1988; United States Patent 4,876,279, issued October 24, 1989; United States Patent 4,847,306, issued July 11, 1989; United States Patent 5,049,696, issued September 17, 1991; European Patent Application EP 245,990, published November 19, 1987; European Patent Application EP 251,625, published January 7, 1988; United States Patent 4,719,229, published January 12, 1988; Japanese Patent Application 63014722, published January 21, 1988; United States Patent 4,736,064, issued April 5, 1988; United States Patent, 4,738,982 issued April 19, 1988; United States Patent 4,845,237, issued July 4, 1989; European Patent EP 306,263, granted March 18, 1992; United States Patent 5,026,708, issued June 25, 1991; United States Patent 4,863, 957, issued September 5, 1989; United States Patent 4,946,841, issued August 7, 1990; European Patent 339358, granted July 13, 1994; United States Patent 4,937,264 issued June 26, 1998; United States Patent 4,876,366, issued October 24, 1989; United States Patent 4,921,974, issued May 1, 1990; United States Patent 4,963,538 issued October 16, 1990; United States Patent 5,130,306, issued July 14, 1992; United States Patent 4,900,754 issued February 13, 1990; United States Patent 5,026,698, issued June 25, 1991; United States Patent 4,977,161, issued December 11, 1990; United States Patent 4,927,851, issued May 22, 1990; European Patent Application EP 373,507, published June 20, 1990; United States Patent 4,939,143, issued July 3, 1990; United States Patent 4,939,159, issued July 3, 1990; United States Patent 4,940,727, issued July 10, 1990; United States Patent 5,116,870, issued May 26, 1992; Australian Patent AU 635,545, granted March 25, 1993; United States Patent 5,098,391, issued March 24, 1992; United States Patent 5,294,724, issued March 15, 1994; United States Patent 5,001,255, issued March 19, 1991; United States Patent 5,149,834, issued September 22, 1992; United States Patent 5,089,523, issued February 18, 1992; European Patent Application EP 465,265 published January 8, 1992; United States Patent 5,476,846, issued December 19, 1995; United States Patent 5,321,046, issued June 14, 1994; United States Patent 5,106,992, issued April 21, 1992; United States Patent 5,347,039, issued September 13, 1994; Japanese Patent Application 4193836, published July 13, 1992; Great Britian patent Application 2253787, published September 23, 1992; United States Patent 5,411,969, issued May 2, 1995; Japanese Patent Application 4,356,435, published December 10, 1992; United States Patent 5,266,707 issued November 30, 1993; United States Patent 5,455,247 issued October 3, 1995; United States Patent 5,475,029, issued December 12, 1995; United States Patent 5,591,772, issued January 7, 1997; United States Patent 5,286,746 issued February 15, 1994; Japanese Patent Application JP 7089898, published April 4, 1995; European Patent Application EP 677,039, published October 18, 1995 and World Patent Application 96/08248, published March 21, 1996.

This invention relates both to methods of treating cancer in which the FTase inhibitor and the HMG CoA reductase inhibitor are administered together, as part of the same pharmaceutical composition, as well as to methods in which these two active agents are administered separately as part of an appropriate dose regimen designed to obtain the benefits of the combination therapy. The appropriate dose regimen, the amount of each dose administered, and specific intervals between doses of each active agent will depend upon the subject being treated, the type of cancer or abnormal cell growth and the severity of the condition. In carrying out the methods of this invention, the FTase inhibitor will be administered in the amounts disclosed in the literature, or otherwise believed to be effective, for the administration of such compound as a single active agent for the treatment of cancer or the inhibition of abnormal cell growth, and the HMG CoA reductase inhibitor will be administered in an amount that is about one quarter to one half of the amount disclosed in the literature, or otherwise believed to be effecive, for administration of such compound as a single agent for the treatment of hypercholesterolemia. For example, in carrying out the present inventions, the FTase inhibitors of formulas I, IIA, IIB and III will typically be admisterered to an average 70 kg adult human in an amount ranging from about 0.005 to about 0.6 mg per kg body weight of the subject being treated per day, in single or divided doses, and the HMG CoA reductase inhibitor atorvastatin will typically be administered in an amount ranging from about 0.07 to about 3.6 mg per kg body weight per day, in single or divided doses. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the above range may be more than adequate, while in other cases dosage levels higher than the above upper daily limit may be employed without causing any harmful side effect, provided that such larger dosages are administered as several small doses for administration throughout the day.

The FTase inhibitors and the HMG CoA reductase inhibitors that are employed in the pharmaceutical compositions and methods of this invention are hereinafter also referred to as "therapeutic agents". The therapeutic agents can be administered via either the oral or parenteral route. Compositions containing both a FTase inhibitor and an HMG CoA reductase inhibitor will generally be administered orally or parenterally daily, in single or divided doses, so that the total amount of each active agent administered falls within the above guidelines.

The therapeutic agents may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules,

lozenges, troches, hard candies, suppositories, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutic compounds of this invention, when administered separately (i.e., not in the same pharmaceutical composition) are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic agent in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The activity of the therapeutic compounds as FTase inhibitors may be determined by their ability, relative to a control, to inhibit Ftase in vitro. This procedure is described below.

A crude preparation of FTase comprising the cytosolic fraction of homogenized brain tissue is used for screening compounds in a 96-well assay format. The cytosolic fraction is prepared by homogenizing approx. 40 grams fresh tissue in 100 ml of sucrose/$MgCl_2$/EDTA buffer (using a Dounce homogenizer; 10-15 strokes), centrifuging the homogenates at 1000 grams for 10 minutes at 4G, re-centrifuging the supernatant at 17,000 grams for 15 minutes at 4G, and then collecting the resulting supernatant. This supernatant is diluted to contain a final concentration of 50 mM Tris HCl (pH 7.5), 5 mN DTT, 0.2 M KCl, 20 mM $ZnCl_2$, 1 mM PMSF and re-centrifuged at 178,000 grams for

90 minutes at 4G. The supernatant, termed "crude FTase" was assayed for protein concentration, aliquoted, and stored at -70°C.

The assay used to measure in vitro inhibition of human FTase is a modification of the method described by Amersham LifeScience for using their Farnesyl transferase (3H) Scintilation Proximity Assay (SPA) kit (TRKQ 7010). FTase enzyme activity is determined in a volume of 100 ml containing 50 mM N-(2-hydroxy ethyl) piperazine-N¢-(2-ethane sulfonic acid) (HEPES), pH 7.5, 30 mM $MgCl_2$, 20 uM KCl, 5 mM Na_2HPO_4, 5 mM dithiothreitol (DTT), 0.01% Triton X-100, 5% dimethyl sulfoxide (DMSO), 20 mg of crude FTase, 0.12 mM [3H]-farnesyl pyrophosphate ([3H]-FPP; 36000 dpm/pmole, Amersham LifeScience), and 0.2 mM of biotinylated Ras peptide KTKCVIS (Bt-KTKCVIS) that is N-terminally biotinylated at its alpha amino group and was synthesized and purified by HPLC in house. The reaction is initiated by addition of the enzyme and terminated by addition of EDTA (supplied as the STOP reagent in kit TRKQ 7010) following a 45 minute incubation at 37°C. Prenylated and unprenylated Bt-KTKCVIS is captured by adding 10 ml of steptavidin-coated SPA beads (TRKQ 7010) per well and incubating the reaction mixture for 30 minutes at room temperature. The amount of radioactivity bound to the SPA beads is determined using a MicroBeta 1450 plate counter. Under these assay conditions, the enzyme activity is linear with respect to the concentrations of the prenyl group acceptor, Bt-KTKCVIS, and crude FTase, but saturating with respect to the prenyl donor, FPP. The assay reaction time is also in the linear range.

The test compounds are routinely dissolved in 100% DMSO. Inhibition of farnesyl transferase activity is determined by calculating percent incorporation of tritiated-farnesyl in the presence of the test compound vs. its incorporation in control wells (absence of inhibitor). IC_{50} values, that is, the concentration required to produce half maximal farnesylation of Bt-KTKCVIS, is determined from the dose-responses obtained.

A fluorsecence assay for FTase activity that can be used to screen for FTase inhibitors is described in UK Patent Application GB 2,267,966, which was published on December 22, 1993.

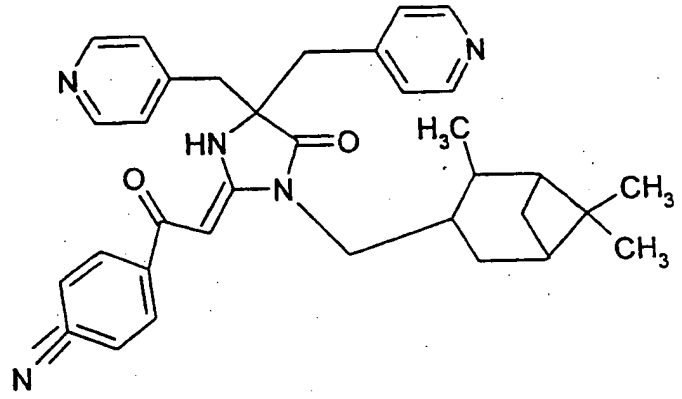
The activity of certain therapeutic agents as HMG CoA reductase inhibitors may be determined by the procedure described by Dugan et al, Achiv. Biochem. Biophys., (1972), 152, 21-27. In this method, the level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet contining 5% cholestyramine for four days, after which the rats are sacrificed. The rat livers are homogenized, and the incorporation of cholesterol-^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC_{50} value.

A second method (designated COR screen) is that described by T. Kita, et al, J. Clin. Invest., (1980), 66: 1094-1100. In this method, the amount of ^{14}C-HMG-CoA converted to ^{14}C-

mevalonate in the presence of a purified enzyme preparation of HMG-CoA reductase is measured. The micromolar concentration of compound required for 50% inhibition of cholesterol synthesis is measured and recorded as an IC_{50} value.

The various methods of this invention may be practiced as part of a therapy that includes the administration of one or more other anti-tumor substances, for example, those selected from mitotic inhibitors, for example, vinblastine; alkylating agents, for example, cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example, 5-fluorouracil, cystosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 239362 such as N-{5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl}-L-glutamic acid; intercalating antibiotics, for example, adriamycin and bleomycin; enzymes, for example, asparaginase; topoisomerase inhibitors, for example, etoposide; biological response modifiers, for example, interferon; and anti-hormones, for example, antioestrogens such as 'NOLVADEX' (tamoxifen) or antiandrogens such as 'CASODEX' (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide. Such therapies may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the therapy. According to this aspect of the invention, there is provided a pharmaceutical product comprising a pharmaceutically acceptable carrier, as described above, one or both of an HMG CoA reductase inhibitor and a FTase inhibitor, and an additional anti-tumor agent, as described above.

As indicated in Table 1 below, the present inventor has shown that the effectiveness of Compound 1, which has the structure



can be enhanced by a minimally effective dose of lovastatin.

TABLE 1

Synergistic Effects of Lovastatin and Compound 1 Treatment on Prenylation of K-*ras* 4B in Intact Cells

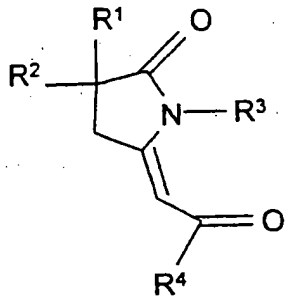
	% Inhibition OF K-Ras 4B Prenylation*	
Compound 1[μm]	CONTROL	+ 5μM Lovastatin
0	0	23
0.1	0	56
1.0	0	83
10	0	96

* Semi-confluent monolayers of the NIH-3T3 tranfectant overexpressing mutant K-Ras 4B were treated for 18 hours at 37C with increasing concentrations of CP-390,392 in the presence and absence of 5 μM of hydrolysed lovastatin. Cells were lysed in a RIPA lysis buffer (50 mM tris[hydroxymethyl] amino-methane, 0.15M sodium chloride, 1% sodium deoxycholate, 1% Triton X-100, 0.1% SDS, 0.25 sodium azide; ph 8.5) containing 1 mM of DTT (dithiothreitol; Boehringer Mannheim, Indianapolis, IN) and protease inhibitors (Aprotinin, Leupeptin, Anitpain, Pefabloc at final concentrations of 10 μg/ml, 2 μg/ml, 2 μg/ml and 50 μM, respectively; Boehringer Mannheim, Indianapolis, IN) and boiled for 3 minutes. Equal amounts of protein (100 μg/lane) were resolved by SDS-PAGE on 12.5% gels and transferred to Immobilon-P membranes (Intergrated Separation Systems, Natick, MA.). The membranes were immunoblotted with 5 μg/ml of anti-Pan-*ras* (Ab-3) monoclonal antibody (Calbiochem, La Jolla, CA). The blots were incubated with peroxidase-conjugated secondary antibody, and the immunoblotted *Ras* protein were detected by enhanced chemiluminescence (Amersham Life Products, Arlington Heights, IL). Percent of prenylated *Ras* was determined by densitometric scanning using MasterScan 3.0 (Scanalytics, Billerica, Massachusettes).

CLAIMS

1. A pharmaceutical composition for the treatment of cancer or a benign proliferative disorder in a mammal, comprising a FTase inhibitor, an HMG CoA reductase inhibitor and a pharmaceutically acceptable carrier, wherein the FTase inhibitor and the HMG CoA reductase inhibitor are present in amounts that render the composition effective in the treatment of cancer or a benign proliferative disorder

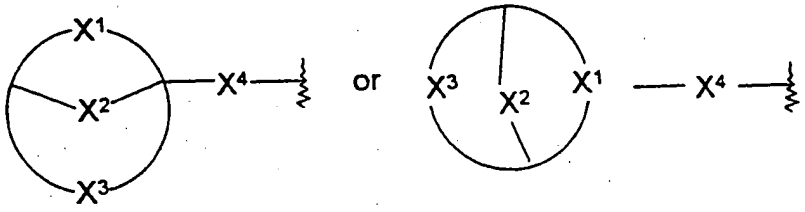
2. A pharmaceutical composition according to claim 1, wherein the FTase inhibitor is selected from: (a) compounds of the formula



I

wherein R^1 and R^2 are independently selected from the group consisting of $-(CH_2)_p$(5-10 membered heterocycles), $-(CH_2)_p(C_6-C_{10}$ aryl), allyl, propargyl and C_1-C_6 alkyl wherein p is 0 to 3, said alkyl and the alkyl moieties of said R^1 and R^2 groups are optionally substituted by 1 to 3 R^9 substituents, and the aryl and heterocyclic moieties of said R^1 and R^2 groups are optionally substituted by 1 to 3 substituents independently selected from halo and R^9;

R^3 is $-(CH_2)_m$(1- or 2-adamantyl), $-(CH_2)_m(C_3-C_{10}$ cycloalkyl), $-(CH_2)_m(C_6-C_{10}$ aryl), C_1-C_{10} alkyl,



(A) (B)

wherein m is 0 to 6, and said cycloalkyl and alkyl optionally contain 1 or 2 double or triple bonds;

X^1, X^2, and X^3 are each independently C_1-C_7 alkylene optionally containing 1 or 2 double or triple bonds, X^4 is a bond or C_1-C_7 alkylene optionally containing 1 or 2 double or triple bonds, and, in formula (B), the X^4 moiety is attached to the X^1 moiety at any available carbon in the X^1 moiety;

R^4 is C_6-C_{10} aryl, 5-10 membered heterocyclyl or C_1-C_6 alkyl wherein each of said R^4 groups is optionally substituted by 1 to 3 R^5 substituents;

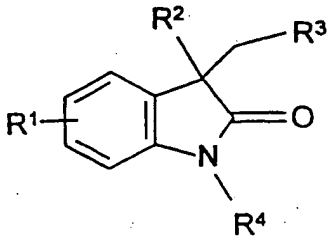
each R^5 is independently selected from the group consisting of halo, nitro, cyano, phenyl, -$C(O)OR^6$, -$SO_2NR^6R^7$, -NR^6R^8, -$C(O)R^6$, -OR^6, -$C(O)NR^6R^8$, -$OC(O)NR^6R^8$, -$NR^8C(O)NR^8R^6$, -$NR^8C(O)R^6$, -$NR^8C(O)O(C_1$-C_4 alkyl), -$C(NR^8)NR^8R^6$, -$C(NCN)NR^8R^6$, -$C(NCN)S(C_1$-C_4 alkyl), -$NR^8C(NCN)S(C_1$-C_4 alkyl), -$NR^8C(NCN)NR^8R^6$, -$NR^8SO_2(C_1$-C_4 alkyl), -$S(O)_n(C_1$-C_4 alkyl) wherein n is 0 to 2, -$NR^8C(O)C(O)NR^8R^6$, -$NR^8C(O)C(O)R^8$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, and C_1-C_4 alkyl optionally substituted by 1 to 3 fluoro substituents;

each R^6 and R^7 is independently hydrogen or C_1-C_4 alkyl;

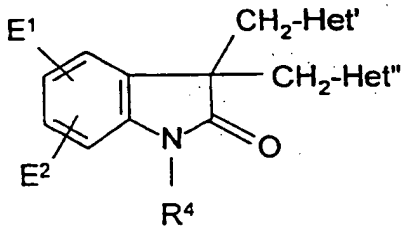
each R^8 is independently R^6 or -OR^6; and,

each R^9 is independently selected from cyano, R^6, -OR^6, -$OC(O)R^6$, -$C(O)OR^6$, -$C(O)NR^6R^7$, -NR^6R^7, -NR^6R^8, -$SO_2NR^6R^7$, and C_1-C_4 alkyl substituted by hydroxy; and

(b) compounds of the formula



or



IIA IIB

wherein R^1 is hydrogen, halo (e.g., chloro, fluoro, bromo or iodo), cyano, hydroxy, nitro, trifluoromethyl, -NHR^5, -NR^5R^5, R^5, -OR^5 or -$S(O)_m$-R^5;

R^2 is -$(CH_2)_n$-Y or -$OCOR^5$;

R^3 is 4-, 3-, or 2-pyridyl, pyrimidyl, pyrazinyl, 2-fluoro-4-pyridyl or 3-fluoro-4-pyridyl;

R^4 is 1-adamantyl or 2-adamantyl;

Y is hydrogen, hydroxy, amino, cyano, -NHR^5, -NR^5R^5, -$NHCOR^5$, -$NHCO_2R^5$, halo, OR^5, -$S(O)_mR^5$, -CO_2H, -CO_2R^5, -$CONR^5R^5$, -$CONHR^5$, -$CONH_2$, -COR^5, -$CH{=}CHCO_2R^5$, -$OCOR^5$, phenyl, phenyl substituted with W, -$C{\equiv}CCO_2R^5$, -$CH{=}CHR^5$ or -$C{\equiv}CR^5$;

each R^5 is, independently, (C_1-C_4) straight or branched alkyl, phenyl or benzyl, wherein said phenyl and the phenyl moiety of said benzyl may optionally be substituted with halo, hydroxy, nitro, cyano, amino, (C_1-C_4) straight or branched alkyl, (C_1-C_4) straight or branched alkoxy, phenyl, benzyl, (C_1-C_4)alkylamino, di[(C_1-C_4)alkyl]amino, or -$S(O)_m$-(C_1-C_4) straight or branched alkyl;

each W is, independently, halo, R^5, hydroxy, -OR^5, nitro, amino, -NHR^5, -NR^5R^5, cyano, or -$S(O)_m$-R^5;

m is 0, 1 or 2;

n is 1 to 7;

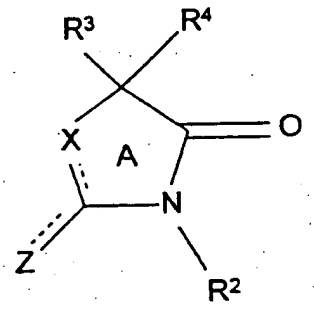
p is 0 or 1;

E^1 and E^2 are selected, independently, from hydrogen, halo, (C_1-C_3)alkyl, hydroxy, (C_1-C_3)alkoxy, nitro, trifluoromethyl, cyano, amino, (C_1-C_3)alkylamino and di[(C_1-C_3)alkyl]amino;

and their pharmaceutically acceptable salts.

Het' and Het'' are selected, independently, from 6 membered heterocyclic rings containing from one to four nitrogen atoms as part of the ring, optionally substituted with one substituent selected from (C_1-C_3)alkyl, halo, hydroxy, (C_1-C_3)alkoxy, amino, (C_1-C_3)alkylamino and di[(C_1-C_3)alkyl]amino; and

(c) compounds of the formula



III

wherein both dotted lines represent optional double bonds;

Z is oxygen or sulfur when it is double bonded to ring A and Z is hydroxy, (C_1-C_{10})alkyl-S-, (C_1-C_{10})alkyl-SO-, (C_1-C_{10})alkyl-SO_2-, adamant-2-yl-S-, naphthyl-S-, benzyl-S-, phenyl-C(=O)CH_2-S-, (C_1-C_6)alkyl-O-C(=O)-CH_2-S- or (H,H) (i.e., Z represents two hydrogen atoms, each of which is single bonded to the same carbon of ring A) when Z is single bonded to ring A, and wherein said naphthyl and phenyl and the phenyl moiety of said benzyl may optionally be substituted with from one to three substituents independently selected from (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), amino, (C_1-C_6)alkylamino, [di-(C_1-C_6)alkyl]amino,

cyano, nitro, (C_1-C_6)alkyl-SO_n- wherein n is zero, one or two, -COOH, -$COO(C_1-C_6)$alkyl and -$C(O)NH(C_1-C_6)$alkyl;

X is NR^1 or CHR^1;

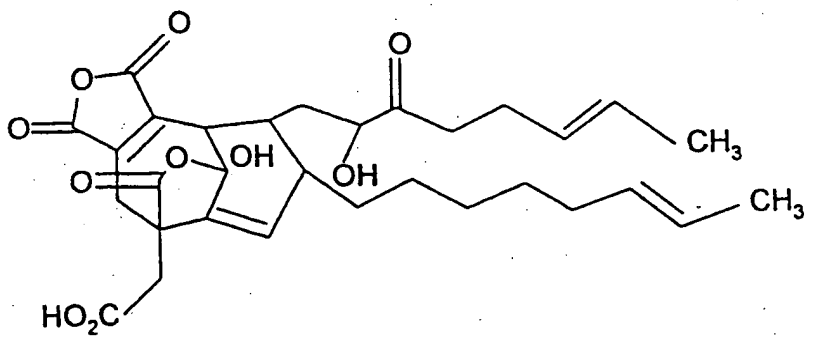
R^1 is hydrogen, (C_1-C_6)alkyl or (C_1-C_6)alkylphenyl when ring A is saturated (i.e., when ring A contains no double bonds) and R^1 is absent when ring A contains a double bond;

R^2 is selected from naphthyl, phenyl, (C_1-C_6)alkylphenyl, 1-adamantyl, 2-adamantyl, (C_1-C_8) straight or branched alkyl, (C_3-C_{10}) cycloalkyl and (C_8-C_{30})bicyclic or tricyclic alkyl; wherein said (C_3-C_{10})cycloalkyl and said (C_8-C_{30})bicyclic or tricyclic alkyl may optionally be substituted with a hydroxy group; and wherein said adamantyl groups may optionally be substituted with from one to three substituents independently selected from (C_1-C_6)alkyl, halo and hydroxy; and

R^3 and R^4 are independently selected from benzyl, wherein the phenyl moiety of said benzyl may optionally be substituted with an amino or nitro group; hydrogen, phenyl, $(N\equiv C)$-(C_1-C_6)alkyl, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl and Het-CH_2, wherein Het is selected from 2-, 3- or 4-pyridinyl, furyl, tetrahydrofuryl, pyrimidyl, pyrazinyl, pyrazolyl, isoxazolyl, thiophenyl and triazolyl;

with the proviso that (a) no more than one of the two dotted lines can represent a double bond in any one compound, (b) when Z is (H, H), X is CH_2, (c) when Z is oxygen or (H, H) and X is CHR^1, R^1 must be hydrogen, (d) when Z is sulfur and X is NR^1, R^1 must be hydrogen, and (e) one of R^3 and R^4 must be Het-CH_2; and

(d) the compound



IV

and the pharmaceutically acceptable salts of the foregoing compounds.

3. A pharmaceutical composition according to claim 1, wherein the HMG CoA reductase inhibitor is selected from the group consisting of atorvastatin, pravastatin, lovastatin, compactin fluvastatin and simvastatin, and the pharmaceutically acceptable salts of the foregoing compounds.

4. A method of treating cancer or a benign proliferative disorder in a mammal, comprising administering to said mammal a pharmaceutical composition according to any one of claims 1 to 3.

5. A method of treating cancer or a benign proliferative disorder in a mammal, comprising administering to said mammal a FTase inhibitor and an HMG CoA reductase inhibitor, wherein the FTase inhibitor and the HMG CoA reductase inhibitor are administered in amounts that render the combination of these two active agents effective in treating cancer or a benign proliferative disorder.

6. A method according to claim 5, wherein the HMG CoA reductase inhibitor is atorvastatin, pravastatin, fluvastatin, simvastatin, lovastatin or compactin, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition for inhibiting the abnormal growth of cells in a mammal, comprising a FTase inhibitor, an HMG CoA reductase inhibitor and a pharmaceutically acceptable carrier, wherein the active ingredients in such composition are present in amounts that render the composition effective in inhibiting the abnormal growth of cells.

8. A method of inhibiting the abnormal growth of cells in a mammal, comprising administering to said mammal an abnormal cell growth inhibiting effective amount of a pharmaceutical composition comprising a FTase inhibitor, an HMG CoA reductase inhibitor and a pharmaceutically acceptable carrier.

9. A method of inhibiting the abnormal growth of cells in a mammal, comprising administering to said mammal a FTase inhibitor and an HMG CoA reductase inhibitor in amounts that render the combination of such two active agents effective in inhibiting the abnormal growth of cells.

INTERNATIONAL SEARCH REPORT

Ir itional Application No
PCT/IB 98/00881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435 //(A61K31/435,31:405),(A61K31/435,31:40),
(A61K31/435,31:365),(A61K31/435,31:22)

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 05902 A (BANYU PHARMA CO LTD ;YONEMOTO MARI (JP); TANAKA KENJI (JP); IWASAW) 20 February 1997 & EP 0 856 315 A (BANYU PHARMA LTD) 5 August 1998 see claims 1-4	1,3-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 1998	24/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 98/00881

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4-6, 8, 9
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 4-6, 8, 9 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No
PCT/IB 98/00881

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705902 A	20-02-1997	EP 0856315 A	05-08-1998